ORIGINAL INVESTIGATION

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Risk factors for orofacial and limbtruncal tardive dyskinesia in older patients: a prospective longitudinal study

Abstract Although there is a consensus that orofacial and limbtruncal subtypes of tardive dyskinesia (TD) exist and may represent distinct pathophysiologic entities, few studies have examined the incidence of and risk factors associated with the development of these TD subtypes. Two hundred and sixty-six middle-aged and elderly outpatients with a median duration of 21 days of total lifetime neuroleptic exposure at study entry were evaluated at 1- to 3-month intervals. Using "mild" dyskinesia in any part of the body for diagnosis of TD, the cumulative incidence of orofacial TD was 38.5 and 65.7% after 1 and 2 years, respectively, whereas that of limbtruncal TD was 18.6 and 32.6% after 1 and 2 years. Preclinical dyskinesia was predictive of both orofacial and limbtruncal TD. History of alcohol abuse or dependence was a significant predictor of orofacial TD only whereas tremor was a significant predictor of limbtruncal TD only. Findings support suggestions that orofacial and limbtruncal TD may represent specific subsyndromes with different risk factors.

Key words Alcohol dependence · Movement disorders · Schizophrenia · Alzheimer's disease · Neuroleptics · Aging

Introduction

Tardive dyskinesia (TD) is an abnormal involuntary movement disorder associated with the use of long-term neuroleptic treatment. To date, the mechanisms underlying this disorder as well as the pathophysiologic factors contributing to it are not well understood

(Casey and Gerlach 1986; Jeste et al. 1986; Kane et al. 1992). One possible explanation for this lack of knowledge is that the heterogeneity of TD may represent various distinct pathophysiological mechanisms. For instance, although TD is typically regarded as a unitary entity, its clinical presentation and course vary considerably. One way to begin to clarify the potentially intricate pathophysiology of TD is to emphasize the clinical heterogeneity in TD to identify subtypes.

Several studies have suggested that TD is composed of at least two major subsyndromes based upon topography of abnormal involuntary movements (viz., orofacial and limbtruncal). In support of this concept are: 1) factor analysis of "blind" clinical ratings suggesting that the dyskinetic movements are best grouped into two syndromes: orofacial and limbtruncal (Kidger et al. 1980; Glazer and Morgenstern 1988); 2) observations of age-related differences in these dyskinesias (i.e., orofacial dyskinesias are more prevalent in older patients whereas limbtruncal dyskinesias are more prevalent in younger patients) (Tarsy et al. 1977); 3) associations of orofacial dyskinesias with positive symptoms in schizophrenia (Waddington and Youssef 1986; Gureje 1988; Sandyk and Kay 1991) and limbtruncal dyskinesias with negative symptoms in schizophrenia (Brown and White 1991); 4) studies reporting greater neuropsychological impairment in patients with limbtruncal (versus orofacial) dyskinesia (Brown and White 1992; Paulsen et al. 1994); 5) neuroimaging studies showing greater frontal blood flow (as assessed by single photon emission computed tomography) and greater caudate atrophy (as assessed by computed tomography) in patients with limbtruncal (as opposed to orofacial) dyskinesias (Mukherjee et al. 1991); 6) a report of an association between limbtruncal, but not orofacial, dyskinesias, and the presence of pineal gland calcification (Sandyk 1990); 7) significant associations of limbtruncal (but not orofacial) dyskinesia and severity of melanocyte-stimulating hormone seborrhea (Sandyk and Pardesh 1990) and 8) studies noting

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differential drug responses between orofacial and limbtruncal dyskinesias (Casey and Denney, 1977; Lieberman et al. 1988a, b).

Prevalence of TD is approximately 24% (Yassa and Jeste 1992). Although numerous surveys have been conducted over the past 3 decades (Baldessarini et al. 1980; Jeste and Wyatt 1982; Kane and Smith 1982; Hansen et al. 1986; Saltz et al. 1991; Jeste et al. 1995), few studies have examined the incidence of TD by topography. In general, approximately 70–100% of TD patients demonstrate orofacial movements, 20–60% have limbtruncal movements, and 11–50% have both orofacial and limbtruncal movements (Jeste and Wyatt 1982; Lohr et al. 1986; Glazer and Morgenstern 1988; Gureje 1989; Paulsen et al. 1994). There are several methodological reasons for the extreme variability and ranges of these estimates: 1) variable criteria for the diagnoses of TD and its subtypes; 2) heterogeneity of patient groups combined in study samples; 3) failure to consider the possible influence of demographic (particularly age) and treatment factors (particularly neuroleptic potency and cumulative amount); 4) failure to assess the independence of these topographical subtypes; and 5) reliance on cross-sectional retrospective designs. Although prevalence surveys help define the scope of the problem, an understanding of the risk factors associated with the production and precipitation of TD can occur primarily through prospective studies of incidence.

Despite clinical and research consensus on the presence of these two subtypes of TD, most studies investigating risk factors for TD have treated it as a unitary syndrome. For instance, previous reports have suggested that increased age (Saltz et al. 1991), mood disorder (Casey 1988), diabetes mellitus (Ganzini et al. 1991b), alcohol dependence (Olivera et al. 1990), smoking (Yassa et al. 1987), ethnicity (Morgenstern and Glazer 1993), extrapyramidal signs (EPS) (Crane 1974), and cognitive impairment (see Paulsen et al. 1994) may increase the risk for TD. Risk factors for TD have been reviewed extensively (see Casey 1988; Gardoes et al. 1988; Kane et al. 1992; Jeste and Caligiuri 1993). The current study was designed to identify the incidence of and risk factors associated with orofacial and limbtruncal TD in older psychiatric outpatients. Data from this project have been reported previously (Jeste et al. 1995) to address the incidence and risk factors for TD in general. Findings revealed that the cumulative incidence of TD [defined using Schooler and Kane (1982) criteria], in general, was 26%, 52%, and 60% after 1, 2, and 3 years, respectively. Specific risk factors for the development of TD were baseline duration of neuroleptic use, cumulative amount of high-potency neuroleptics, history of alcohol abuse or dependence, minimal or borderline dyskinesia at baseline, and tremor on instrumental assessment. The present report compares the development of orofacial and limbtruncal TD, using a lower threshold for diagnosis

of TD (i.e., at least one rating of "mild" instead of a minimum of two ratings of "mild" or one rating of "moderate" dyskinesia as in the criteria of Schooler and Kane (1982). While the Schooler and Kane (1982) criteria are useful for research purposes, leniency in the diagnosis of TD is important for early identification and management. Indeed, the DSM-IV (American Psychiatric Association 1994) does not include any severity criterion for diagnosis of TD in order to facilitate early detection and possible reversibility of TD.

Materials and methods

Subjects

Subjects were 266 outpatients previously reported (Jeste et al. 1995) as meeting the following criteria: (1) absence of TD at baseline as defined by Schooler and Kane's (1982) criteria, (2) presence of a DSM-III-R (American Psychiatric Association 1987) psychiatric disorder (confirmed by two board certified psychiatrists) for which treatment with neuroleptic medications was indicated, (3) absence of severe physical illnesses that would preclude clinical, cognitive, or instrumental motor assessment, (4) availability for evaluation prior to or early in the course of neuroleptic treatment, (5) age over 45 years, (6) availability of medical and psychiatric history (including past neuroleptic use), and (7) willingness to participate and sign informed consent. Subjects were recruited over a 4-year period from a variety of sources, but the majority were patients at the San Diego Veterans Affairs Medical Center.

As stated above, the orofacial and limbtruncal TD criteria employed in the current investigation were less stringent than the criteria for general TD employed in the prior report. Twenty-two of the 266 subjects met the current criteria for orofacial TD at baseline, and were thus excluded from the orofacial TD survival analyses. Similarly, a nonoverlapping group of 9 of the 266 subjects met the current criteria for limbtruncal TD at baseline, and were thus excluded from the limbtruncal TD survival analyses. Details of the demographic makeup of the final samples for the limbtruncal and orofacial survival analyses are provided in Table 1.

Table 1 Demographic description of initial subject pool for orofacial and limbtruncal tardive dyskinesia survival analyses

	Orofacial ($n = 244$)	Limbtruncal ($n = 257$)
Age in years: mean (SD)	65.8(12.1)	65.6 (12.2)
Education in years: mean (SD)	12.4(3.4)	12.4 (3.4)
Gender		
% Males	80.7%	81.6%
% Females	19.3%	18.4%
Diagnosis		
% Dementia	25.8%	25.3%
% Organic	15.2%	15.6%
% Schizophrenia	18.9%	21.8%
% Mood disorders	21.7%	19.8%
% Other non-organic	18.4%	17.5%
Ethnicity		
% Caucasian	83.6%	82.4%
% African American	8.6%	8.6%
% Hispanic	4.9%	5.9%
% Asian American	2.0%	2.3%
% Other	0.8%	0.8%

Procedures

Procedural details have been described previously (Jeste et al. 1995), but will be briefly reviewed here. The initial evaluation included the following: (a) complete neurological, other medical, and mental status examinations; (b) review of patients' pharmacologic history; (c) administration of psychiatric and motor rating scales; and (d) instrumental assessment of motor function. Medical and psychiatric diagnosis were made by a consensus of two psychiatrists board certified in Geriatric Psychiatry following a multidisciplinary staffing of each patient. Follow-up evaluations were scheduled at 1 and 3 months post-entry, and then once every 3 months. These follow-up evaluations included: (a) review of pharmacotherapy administered since the previous assessment, (b) psychiatric and motor ratings, (c) gross assessment of global cognitive functioning [Mini Mental State Examination (MMSE; Folstein et al. 1975)], and (d) instrumental motor assessments. All rating scales and standardized assessments were completed by non-treatment team personnel who were kept "blind" to other clinical information.

TD Assessment

TD diagnoses were established using the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health 1975). Orofacial TD was diagnosed when at least one rating of 2 (definite but mild) or more was present on any of the first four (i.e. lips, tongue, jaw, face) AIMS items. Limbtruncal TD was diagnosed when a rating of 2 or more was present on any of the AIMS items 5, 6 or 7 (i.e., upper extremity, lower extremity, trunk). Although not used in diagnosing TD, the AIMS Global TD Rating was employed among the predictor variables (see below). High inter-rater reliability (intra-class correlation coefficient > 0.84) was established for the AIMS using standardized videotapes and expert consultation.

Psychiatric and motor ratings

Psychiatric ratings included the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962, 1988), and the Hamilton Depression Rating Scale (HAM-D; Hamilton 1967). In addition to the AIMS, motor rating scales included the Simpson-Angus' Scale for early EPS (Simpson and Angus 1970), and Simpson's Abbreviated Dyskinesia Rating Scale (ADRS; Simpson et al. 1979).

Instrumental motor assessment

Baseline and follow-up evaluations included instrumental assessments of motor dysfunction (Çaligiuri et al. 1991a, b). Postural tremor of the upper extremity and hand and jaw dyskinesia were quantified using measures of force instability. Bradykinesia was quantified by measuring the peak instantaneous velocity associated with simple ballistic movements of the wrists. Rigidity was measured to quantify abnormalities in wrist muscle tone (viz., stiffness).

Treatment

Upon study entry a majority of the subjects were randomly assigned to either a high-potency or a low-potency neuroleptic (usually haloperidol or thioridazine, respectively), unless contraindicated by history of allergy or adverse effects, or refused by the patient, caregiver, or physician. For these reasons, a number of patients could not be randomized. Overall, twice as many patients were treated with high-potency neuroleptics as with low-potency ones. Whenever possible, patients remained on the same neuroleptic as long as clinically indicated. For the sake of comparison, all neuroleptic dosages were converted to mg chlorpromazine equivalents (CPZE; Jeste and Wyatt 1982). The average neuroleptic dose was 150 mg CPZE. Moderate to severe extrapyramidal symptoms (EPS) were treated with benztropine mesylate (usually at doses of 2 mg per day or less).

Statistical methods

The cumulative incidence rates of limbtruncal and orofacial TD were assessed via Life Table Survival Analysis (Cutler and Ederer, 1958; Concato et al. 1993). Effects of risk factors on the occurrence of orofacial or limbtruncal TD were investigated with Cox regression analyses (Cox 1972) employed using BMDP software (Dixon 1992).

Fixed (f) and time dependent (t) predictors

Potential predictor variables (risk factors) were considered to be either fixed (f) or time-dependent (t). The values of fixed variables did not change from those observed at baseline. Fixed variables included: gender, age at study entry, education, ethnicity, marital status, diagnosis, duration of prior neuroleptic use, history of alcohol abuse or dependence, diabetes mellitus, and smoking.

Time-dependent variables could potentially change at each follow-up visit. Two of these (t) variables were based on cumulative neuroleptic amount (cumulative amount of high-potency neuroleptics, and cumulative amount of low-potency neuroleptics) and were redefined repeatedly from the baseline visit to the visit on which the target type of TD occurred (or in non-TD patients, from baseline to the last visit). For example, to estimate the risk of orofacial TD at the 9-month visit, we used a patient's cumulative high- and low-potency neuroleptic amounts through the 9-month visit. Thus, the cumulative amount variables were "contemporary (t) variables." With the exception of these two cumulative amount variables, all the (t) variables were redefined up to the visit prior to the occurrence of target type of TD (or the visit prior to the last visit). These "one-visit-back (t) variables" included: MMSE total, AIMS Global TD Rating, ADRS total, Simpson Angus EPS Scale total, BPRS subscale scores for depression, disorganization, hostility, and negative symptoms, HAM-D total, instrumental tremor, instrumental rigidity, instrumental bradykinesia, and instrumental dyskinesia.

Three (t) variables had extremely large ranges and highly skewed distributions (cumulative high-potency amount, cumulative low-potency amount, and neuroleptic use duration at baseline), and so were transformed via a base 10 logarithmic function in order to obtain useful beta (β) coefficients (Dixon, 1992).

Risk factor sets and regression stages

Univariable regression analyses were run for each potential predictor of orofacial and limbtruncal TD. The sample sizes of specific variables varied widely due to variation in the amount of missing data. In order to accommodate the tradeoff between sample size and number of potential predictors, a staged approach to Cox regression was employed (as described previously by Jeste et al. 1995) within each combination of TD type (orofacial and limbtruncal). Backward stepwise Cox regression analyses were run in five stages where significant variables were carried forward to each subsequent stage. Significance of new main effects and interactions was made at criterion $\alpha = 0.01$. Previously identified effects were retained in models if they maintained a trend ($\alpha = 0.10$).

The variables were organized into the following five conceptual groupings, ordered by the original sample sizes for the full pool of 266 subjects:

1. *Demographics* (ns = 257–266): age at study entry, gender, ethnicity, education, marital status, diagnosis, MMSE score, neuroleptic duration at baseline, and high-potency and low-potency neuroleptic amount variables.
2. *Health indices* (ns = 230–266): history of diabetes mellitus, smoking, and alcohol abuse or dependence.
3. *Motor abnormality ratings* (ns = 220–266): AIMS Global Rating (Item 8), ADRS Total, Simpson Angus EPS Scale Total.
4. *Psychiatric ratings* (ns = 191–202): BPRS hostility, depression, disorganization, and negative symptoms subscale scores, and HAM-D total.
5. *Instrumental motor measures* (ns = 153–178): tremor, dyskinesia, bradykinesia, rigidity.

Results

Incidence of orofacial and limbtruncal TD

The orofacial and limbtruncal TD survival curves, and their 95% confidence intervals, are shown in Figs 1 and 2, respectively. The orofacial TD survival rate at 1 and 2 years was 61.5% and 34.3%, respectively. Thus, the 1-year incidence of orofacial TD was 38.5%, and the 2-year incidence was 65.7%. The limbtruncal TD survival rate at 1 and 2 years was 81.4% and 67.4%, respectively. Thus, the 1- and 2- year cumulative incidences of limbtruncal TD equaled 18.6% and 32.6%, respectively.

Univariable predictors of orofacial and limbtruncal TD

Significant results of the univariable analyses are listed in Table 2. The variables which significantly predicted orofacial TD in univariable analyses were: history of alcohol abuse/dependence, one-visit-back AIMS global score, and one-visit-back ADRS total. Although not statistically significant, there was a trend for cumulative high-potency neuroleptic amount in the prediction of orofacial, but not limbtruncal TD. A significant univariable predictor of limbtruncal TD was the one-visit-back tremor.

Fig. 1 Survival curves for orofacial TD onset with 95% confidence intervals (total $n = 266$)
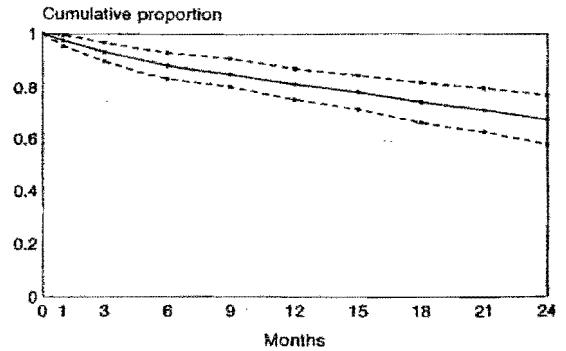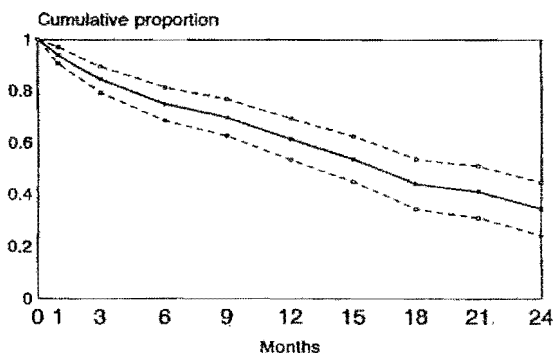

Fig. 2 Survival curves for limbtruncal TD onset with 95% confidence intervals (total $n = 266$)

Cumulative multivariable analyses

Predictors of orofacial TD

Significant results of the (f) and (t) models of orofacial TD risk are shown in Table 3. History of alcohol abuse or dependence was significant in the (f) model. History of alcohol abuse/dependence and the one-visit-back global AIMS score were significant in the (t) model. No significant interactions were observed at any stage. As noted in the univariable analysis, cumulative high-potency neuroleptic amount demonstrated a trend level ($P < 0.10$) of significance in predicting orofacial TD.

Predictors of limbtruncal TD

Significant results of the (f) and (t) models of limbtruncal TD risk are shown in Table 4. The baseline AIMS global score was significant in the (f) model whereas the one-visit-back AIMS global score and one-visit-back tremor scores were significant in the (t) model. No significant interactions was observed.

Relative risk

The natural antilog of the regression coefficient is equivalent to the increased risk associated with a one unit increase in the predictor variable (Collett 1994). Thus, in the case of binary categorical predictor variables, β can be directly interpreted as relative risk. For example, as shown in Table 2, the β associated with a history of alcohol abuse or dependence as a univariable predictor of orofacial TD was equal to 0.6016. The natural antilog of β, (e^{β}), equals 1.83. Thus, a patient with a history of alcohol abuse or dependence had 1.83 times higher risk of developing orofacial TD compared to a patient without a history of alcohol abuse or dependence.

Discussion

We found a much higher (38.5%) cumulative annual incidence of orofacial TD compared to that of

Table 2 Significant univariable predictors of onset of orofacial or limbtruncal tardive dyskinesia. *AIMS* Abnormal Involuntary Movement Scale; *ADRS* Abbreviated Dyskinesia Rating Scale. The relative risk is the estimated change in the risk of TD when the value of the predictor is increased by 1 unit

Type of TD	Variable name	n	β	SE	Relative risk	p
Orofacial						
	(f) Alcohol abuse dependence	244	0.6016	0.2228	1.83	0.008
	(t) AIMS global score	243	0.5496	0.1971	1.73	0.008
	(t) ADRS total	225	0.1245	0.0434	1.13	0.007
Limbtruncal						
	(t) Tremor	146	0.0303	0.0111	1.03	0.009

Table 3 Significant multivariable predictors of onset of orofacial tardive dyskinesia. *AIMS* Abnormal Involuntary Movement Scales; *ADRS* Abbreviated Dyskinesia Rating Scale. The relative risk is the estimated change in the risk of TD when the value of the predictor is increased by 1 unit

Model type	Variable name	n	β	SE	Relative risk	p
Fixed	(f) Alcohol abuse/dependence	244	0.6016	0.2228	1.82	0.008
Time-dependent	(f) Alcohol abuse/dependence	243	0.6047	0.2244	1.83	0.008
	(t) AIMS global score	243	0.8430	0.1752	2.32	0.001

Table 4 Significant multivariable predictors of onset of limbtruncal tardive dyskinesia. *AIMS* Abnormal Involuntary Movement Scales. The relative risk is the estimated change in the risk of TD when the value of the predictor is-increased by 1 unit

Model type	Variable name	n	β	SE	Relative risk	p
Fixed						
	(f) AIMS global score	256	0.5262	0.2003	1.69	0.013
Time dependent						
	(t) AIMS global score	178	0.5813	0.2294	1.79	0.016
	(t) Tremor	178	0.0318	0.0114	1.03	0.007

limbtruncal TD (18.6%) in psychiatric outpatients with a mean age of 66 years being treated with relatively low daily doses of neuroleptics (i.e., average 150 mg CPZE). To our knowledge, this is the first report of the incidence of orofacial and limbtruncal TD to be published.

One problem often encountered by researchers investigating subsyndromes of TD is the overlap, or group of patients displaying both types of TD, which obscures findings regarding pathophysiology, course and outcome of specific subgroups. In the current study, 10% of patients with TD had dyskinesia only affecting limbtruncal topography, whereas over half (i.e., 57%) of TD patients had involvement of orofacial areas only. The remaining one-third of TD patients had dyskinesia involving both orofacial and limbtruncal areas. Of those patients who developed limbtruncal TD, at least 77% also developed orofacial TD. In contrast, only 37% of patients who developed orofacial TD also had limbtruncal TD. In general, these estimates are consistent with other reports of prevalence (Casey and Gerlach 1986; Jeste and Wyatt 1982).

A major finding of the current study was that significant predictors for TD differed depending on the subtype of TD being examined. Although preclinical movement abnormalities (as determined by the AIMS global score) were significant predictors for both orofacial and limbtruncal TD, having a history of alcohol abuse/dependence was only predictive of orofacial TD whereas having EPS such as tremor was only predictive of limbtruncal TD. These unique predictors may suggest differences in the underlying pathophysiology of these TD subtypes.

We found a discrepancy between clinical and instrumental measures of EPS as risk factors of TD. Items from the Simpson-Angus' EPS rating scale, which included ratings of tremor, rigidity, and bradykinesia (in this modified version of the scale), were not predictive of limbtruncal TD, whereas the instrumental measure of tremor was. There are at least three explanations for this discrepancy. First, the added sensitivity offered by the instrumental measure relative to the clinical ratings suggests that patients with subclinical EPS, not necessarily overt EPS, may be at risk for developing limbtruncal TD. Second, the Simpson-Angus' scale rates the severity of resting tremor whereas our instrumental measure is highly sensitive to postural tremor. While resting and postural tremors may be phenomenologically related, especially in early Parkinson's disease (Koller et al. 1989), our findings suggest that the postural tremor may be mechanistically related to TD. Third, by including the total Simpson-Angus' Scale score in the regression models for TD, we may

have inadvertently diluted the relative importance of a single motor sign (e.g., tremor, rigidity, bradykinesia, etc.) for the prediction of TD onset. It is possible that a composite score may not reflect the same physiologic abnormality across a large sample of patients. The specificity of a single instrumental measure is more likely than a composite score to reflect the status of a single pathophysiologic precondition across patients.

Several previous studies have found a higher-than-expected prevalence of TD in patients with a history of alcohol abuse/dependence (Wolf et al. 1985; Olivera et al. 1990; Dixon et al. 1992; Lucey and Dinan, 1992; Duke et al. 1994). Although most investigations failed explicitly to examine the differential effects of alcohol on the topography of TD, some of these studies suggested a propensity for orofacial TD in patients with alcohol abuse or dependence (Olivera et al. 1990). For instance, Lucy and Dinan (1992) noted that patients with orofacial TD had a significantly longer duration of alcohol abuse than those without orofacial TD. Similarly, Duke et al. (1994) reported a significant positive correlation between highest-ever alcohol intake and orofacial TD; no such association was found between limbtruncal TD and alcohol intake or dependence.

It is well established that central nervous system (CNS) deficits are associated with chronic alcoholism (Oscar-Berman 1987). Brain dysfunction in alcoholic subjects has been shown using computerized tomography (Wilkinson 1987), evoked brain potentials (Porjesz and Begleiter 1987; Williams 1987), cerebral blood flow (Risberg and Berglund 1987; Shaw 1987), magnetic resonance imaging, and neuropsychological assessment (Butters et al. 1985; Grant 1987). In an effort to understand the CNS changes associated with alcoholism, there is a large body of work done on the "premature aging hypothesis" of alcoholism (Casey and Denney 1977; Ryan and Butters 1980; Oscar-Berman 1987). Briefly, the premature-aging hypothesis (in its various versions) suggests that alcoholism accelerates aging, beginning either at the onset of heavy drinking or later in life, after the normal manifestations of aging have begun to appear. Although little is understood about the specific neurons and/or neurotransmitter systems susceptible to the interaction of alcohol and aging, some investigations have implicated the cholinergic system (Arendt et al. 1983). This is particularly interesting in light of suggestions that orofacial dyskinesia is the result of damage to the numerically less common cholinergic Aspiny II cells in the basal ganglia (Lohr et al. 1986; Mahadik et al. 1988) and older reports that cholinergic agents improved orofacial dyskinesia to a much greater degree than limbtruncal dyskinesia (Klawans and Rubovits 1974).

Limbtruncal TD was significantly predicted by the instrumental tremor and the one-visit back AIMS Global score. Although it could be argued that clinical and instrumental motor measures are analogous to the primary outcome measure (viz., TD) the question of independence of the pre-diagnostic indicators was of concern. Regarding the instrumental measures of tremor and dyskinesia, we have established previously that spectral analyses of steady-state hand force error distinguish well between tremor and dyskinesia (Caligiuri et al. 1991a) and as such provide assessment of independent pre-diagnostic indicators. Interestingly, our findings are consistent with previous reports linking early EPS to increased incidence of TD (Crane 1972; Casey and Gerlach 1986; Kane et al. 1988). Caligiuri and Lohr (1993) reported that tremor amplitude worsened within 45 min of a single dose of levodopa in patients with dyskinesia. This association between resting tremor and dyskinesia after exposure to levodopa may indicate at least some common pathophysiologic mechanism/s for these hyperkinetic movement disorders. Caligiuri and Lohr (1993) suggest that drug-induced dyskinesia may be related to the extent of nigrostriatal damage, especially loss of the numerically more common γ-aminobutyric acid-releasing Spiny I neurons in the neostriatum (Lohr et al. 1986). This hypothesis is consistent with that of Schneider (1989), who observed that levodopa-induced dyskinesia appeared earlier in MPTP-treated primates who sustained massive striatal dopamine loss compared with animals who sustained less severe dopamine loss. Similarly, Mukherjee et al., (1991) found that subjects with limbtruncal dyskinesia had greater caudate atrophy and greater frontal blood flow than patients with orofacial TD.

Our previous report (Jeste et al. 1995) found that high amounts of high-potency neuroleptics constituted a risk factor for TD (irrespective of subtype). There was a trend-level significance ($p < 0.10$) for high-potency neuroleptic amount to be a risk factor for orofacial TD in the current study. Given that we had a much greater number of patients with orofacial (rather than limbtruncal) TD, it is difficult to determine whether the trend-level significance of high-potency neuroleptics suggests a specific risk factor for orofacial TD or whether it is a risk factor for TD, in general, that would be evident with an increased sample size. .Findings from the current study are unable to address the potential importance of neuroleptics in the development of distinct subtypes of TD.

Some previous reports have found diabetes mellitus to be a significant risk factor for TD (Ganzini et al. 1991a; Sewell et al. 1992; Woerner et al. 1993). Although nonsignificant, it is interesting to note that having diabetes mellitus had a risk ratio of only 1.07 for orofacial TD and a ratio of 1.62 for limbtruncal TD. The role of diabetes mellitus as a specific risk factor for limbtruncal TD needs further evaluation.

There are some limitations to the current study. First, the lack of significant prediction of TD risk by certain variables might be related to relatively small

sample sizes for specified subgroups of subjects (e.g., women, noncaucasians, patients with diabetes). Second, our results may not be generalizable to a population under the age of 45, or one including predominantly nonveteran or female subjects. Third, our cognitive assessment was confined to a brief mental status screen; comprehensive neuropsychological evaluation may elucidate unique cognitive predictors of orofacial and limbtruncal TD. Fourth, although we tried our best to obtain complete information on neuroleptic history and usage, data may be compromised by reliance on accurate reporting of past events. Consequently, we cannot be certain that our sample did not include previously unrecognized or spontaneous (now masked) dyskinesia at baseline (Khot and Wyatt 1991). Finally, there was an annual dropout rate of 20%, although the dropouts appeared to be similar to the study completers on most predictive variables examined. Despite these limitations, our findings are consistent with the notion that orofacial and limbtruncal TD may represent specific subsyndromes with somewhat distinct risk factors.

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